Is there evidence for disease-specific antigens?

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Mtb infection outcome

Index TB case

Community

Latent TB

Active TB

~1 - 2 years

Immunity
Genetics
Antibiotics
etc

BioRender.com
Distinct *Mtb* antigens are associated with infection outcomes

- Longitudinal cohorts (ACS and GC6-74 cohorts)
  - Well-characterized with definite clinical outcomes
- Computational/Systems biology

Munyaradzi M et al 2023
Distinct *Mtb* antigens are associated with infection outcomes

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Clone ID</th>
<th>CDR3a</th>
<th>TRAV</th>
<th>TRAJ</th>
<th>CDR3β</th>
<th>TRBV</th>
<th>TRBJ</th>
<th>HLA-a</th>
<th>HLA-b</th>
<th>Epitope</th>
<th>Protein</th>
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<td>Rv1195(PE13)</td>
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<td>Progressor</td>
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</tbody>
</table>

Do these antigens induce different immune responses?

If so, at what point do the responses diverge into controller vs progressor groups?

Munyaradzi M et al 2023
Distinct *Mtb* antigen immune responses precede development of confirmed TB disease

Swiss HIV Cohort
Matched by age, sex, BMI, CD4 cell count, HIV viral load.

- **Culture**
- **PCR**

**Novel Mtb antigens**
(Rv0081, Rv1733c, Rv2031c, Rv0867c, Rv2389c, Rv3407, Rv2346/47c, Rv2431c, Rv3614/15c, and Rv3865)

Cytokines in cell supernatants
GM-CSF, IFN-γ, IP-10, IL-1RA, IL-6, TNF-α

Meier NR et al 2021
Distinct *Mtb* antigen immune responses precede development of confirmed TB disease

**TABLE 2** | Discriminatory potential of antigen-cytokine in cases and controls at T3 and T4.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Cytokine</th>
<th>TP</th>
<th>TB</th>
<th>n</th>
<th>Controls</th>
<th>n</th>
<th>p-value</th>
<th>AUROC (95% CI)</th>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tr>
<td>Rv2431c</td>
<td>IP-10</td>
<td>T4</td>
<td>6.0 (1.2–159.8)</td>
<td>8</td>
<td>−9.2 (−6.8–3.2)</td>
<td>7</td>
<td>&lt;0.004</td>
<td>0.929 (0.800–1)</td>
<td>2.2</td>
<td>0.87</td>
<td>1</td>
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<tr>
<td>Rv3614/15c</td>
<td>IP-10</td>
<td>T4</td>
<td>8.6 (0.6–238.8)</td>
<td>8</td>
<td>−0.7 (−9.3–4.7)</td>
<td>7</td>
<td>&lt;0.002</td>
<td>0.964 (0.881–1)</td>
<td>5.4</td>
<td>0.87</td>
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<tr>
<td>Rv2031c</td>
<td>TNF-α</td>
<td>T4</td>
<td>9.2 (57.3–2381.0)</td>
<td>8</td>
<td>304.1 (−72.9–103.1)</td>
<td>8</td>
<td>&lt;0.002</td>
<td>0.953 (0.862–1)</td>
<td>72.9</td>
<td>0.87</td>
<td>1</td>
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<tr>
<td>Rv2346/47c</td>
<td>TNF-α</td>
<td>T4</td>
<td>115.5 (6.8–1004.0)</td>
<td>8</td>
<td>−38.4 (−389.9–96.6)</td>
<td>8</td>
<td>&lt;0.002</td>
<td>0.937 (0.824–1)</td>
<td>25.3</td>
<td>0.87</td>
<td>1</td>
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<tr>
<td>Rv2031c</td>
<td>TNF-α</td>
<td>T3</td>
<td>185.6 (46.5–1390.6)</td>
<td>7</td>
<td>2.6 (−814.1–447.7)</td>
<td>9</td>
<td>&lt;0.004</td>
<td>0.921 (0.76–1)</td>
<td>36.3</td>
<td>1.0</td>
<td>0.89</td>
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</table>

Median concentrations of cytokines (pg/ml) and ranges (in parenthesis) induced by stimulation of lymphocytes overnight and ability to discriminate between TB group and control group. AUROC, Area under the receiver operating characteristics.

Dominant TNF-α has previously been shown to discriminate LTBI from ATB Harari et al 2011

Meier NR et al 2021
Distinct *Mtb* antigens determine CD4 T cell differentiation

Household contacts (QFT+/HIV-) of confirmed index TB case (smear+/Xpert med/high)

2 sets of distinct *Mtb* antigens: ‘conserved’ vs ‘variable’ T cell epitope
Mtb antigens under evolutionary selection skew T cells towards Th17 phenotype

Ogongo, Ernst et al Unpublished
Correlates of protective immunity against TB disease

Need to **identify antigens that elicit responses that differentiate progressors from non-progressors**

**What is the right T cell signature?**

- **Characteristics of T cell signature**
  - Antigen specificity

- **Antigen presentation**
  - APC
  - MHC/HLA II
  - Epitope peptide
  - TCR
  - CD4
  - CD28 co-receptor

- **T cell phenotype**
  - *T_h* subset
  - Memory state
  - Maturation/inhibitory receptors

- **Functionality**
  - Secreted cytokines
  - Membrane effectors
  - Cytotoxic molecules
  - Trafficking

**Ogongo and Ernst 2023**

- An effective vaccine against TB should elicit a combination of T cell characteristics

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**What is the contribution of cytokine milieus?**

**What is the role of bystander or uninfected APCs (antigen export)?**
Conclusions and existing gaps

- Distinct *Mtb* antigens are associated with infection outcomes
- Responses to distinct antigens can precede the development of TB disease
- Distinct *Mtb* antigens can determine human T cell differentiation pattern
- Do *Mtb* antigens associated with progression or control induce different immune responses?
- What is the contribution of cytokine milieux in determining *Mtb* antigen-specific T cell responses?
- What is the role of bystander or uninfected APCs (antigen export) in T cell activation?
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